UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: June 20, 2001

MEMORANDUM

SUBJECT: **DIURON**: Report of the Hazard Identification Assessment Review Committee

FROM: Yung G. Yang, Ph.D.
Toxicology Branch
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair
and
Elizabeth Doyle, Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Diana Locke, Ph.D.
Risk Assessor, RRB2
Health Effects Division (7509C)

PC CODE: 035505

On May 29, 2001, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) convened to review the toxicology data base of diuron for hazard identification and to select doses and endpoints for acute dietary, chronic dietary (RfD) as well as occupational and residential exposure assessments and to address the sensitivity of infants and children from exposure to diuron as required by the Food Quality Protection Act (FQPA) of 1996. The HIARC's conclusions are presented in this report.

Committee Members in Attendance

Members in attendance: Ayaad Assaad, Jonathan Chen, Pamela Hurley, Jess Rowland (Chair), David Nixon, Brenda Tarplee, and Yung Yang.

Members in absentia: William Burnam, Elizabeth Doyle, and Elizabeth Mendez.

Also, in attendance: Paula Deschamp, Diana Locke, Alberto Protzel, John Punzi, Renee Sandvig, and Ibrahim Abdel-Saheb (EFED)

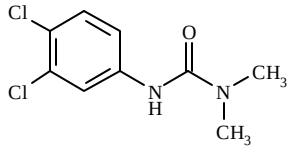
Data evaluation / presentation: _____

Yung G. Yang
Toxicology Branch.

INTRODUCTION

Diuron is a substituted urea herbicide for the control of a wide variety of annual and perennial broadleaves and grassy weeds on both crop and noncrop sites. Its main use is as a pre-emergent, soil applied herbicide, but it can also be used to control emerged weeds. Diuron is available as a technical material, at 95-98% active ingredient or as a manufacturing use product containing 80% diuron for formulation of diuron end-use formulations or as manufacturing use products. As a sole active ingredient, diuron is available in wettable powder, granular, flowables, pelleted/ tableted, liquid suspensions, and soluble concentrate formulations. The exposure duration is expected to be short term for residential uses and short and intermediate term for occupational uses.

Empirical formula: $C_9H_{10}Cl_2N_2O$
Molecular weight: 233.1
CAS Registry No.: 330-54-1
PC Code: 035505



The toxicology data base of diuron has been evaluated by the Health Effects Division RfD Review Committee on September 26, 1996 and the Carcinogenicity Peer Review Committee on December 12, 1996. A Section 18 exemption for the use of diuron 80W in catfish ponds in Mississippi has been issued on May 13, 1999 after brief reviews by the HIARC on March 18, 1999 and FQPA Safety Factor Committee on March 22, 1999. Since then, the toxicology data base of diuron has been re-reviewed and updated by the Toxicology Branch for a Reregistration Eligibility Decision (RED).

On May 29, 2001 the HIARC reviewed the toxicology data base of diuron for hazard identification and to select doses and endpoints for acute dietary, chronic dietary (RfD) as well as occupational and residential exposure assessments in support of a RED and to address the sensitivity of infants and children from exposure to diuron as required by the Food Quality Protection Act (FQPA) of 1996. The HIARC's conclusions are as follows.

1. HAZARD IDENTIFICATION

1.1 Acute Reference Dose (RfD)

Study Selected: None

MRID No.: N/A

Executive Summary: N/A

Dose and Endpoint for Establishing RfD: N/A

Uncertainty Factor (UF): N/A

Comments about Study/Endpoint/Uncertainty Factor: No appropriate effects attributed to a single exposure (dose) was identified including in the rat or rabbit developmental toxicity study. It should be noted that at the 5/13/99 HIARC meeting for Section 18 Exemption, a NOAEL of 16 mg/kg/day from a rat developmental study with an uncertainty factor of 100 was selected for the acute reference dose based on decreased maternal body weight (beginning at gestation day 9) and food consumption (during gestation day 6-10) at 80 mg/kg/day (LOAEL). This dose/endpoint was selected to provide a conservative risk assessment for that action. However, at this meeting (5/29/01) the HIARC determined that it is unlikely that one dose will cause body weight decrease. In addition, there was no developmental or neurotoxic concern for diuron; therefore, no hazard was identified and quantitative risk assessment is not required.

Acute RfD = N/A

1.2 Chronic Reference Dose (RfD)

Study Selected: Chronic toxicity/carcinogenicity study- rats Guideline #: 870.4300

MRID No.: 40886501, 43871901,43804501,44302003

Executive Summary: In a chronic toxicity/oncogenicity study (MRID 40886501; supplementary data provided in MRIDs 43871901, 43804501, and 44302003), diuron (98.7% a.i.; batch no. 232114080) was administered to groups of 60 male and 60 female Wistar rats at dietary concentrations of 0, 25, 250, or 2500 ppm (0, 1.0, 10, or 111 mg/kg/day, respectively, for males

and 0, 1.7, 17, or 202 mg/kg/day for females, respectively) for up to 24 months. At 12 months, 10 animals/sex/group were sacrificed for interim evaluation.

Treatment with diuron did not affect the survival of rats. The only reported treatment-related clinical sign was reddish discolored or bloody urine in high-dose males. A significant decrease in body weight was seen in both sexes of high-dose rats (12-15% for males; 6-14% for females, $p<0.01$) throughout the study. Body weight gains were similarly depressed, the total gains for high-dose males and females were 82 and 79% of controls, respectively. The slight decreases in body weights and weight gains of mid-dose males (4-6%; $p<0.05$ or 0.01) were not biologically significant. Food consumption was unaffected but overall food efficiency was lowered for high-dose males and females (86% and 76% of controls, respectively).

Diuron affected hematopoietic system resulting in hemolytic anemia and compensatory hematopoiesis, which were manifested as significantly decreased ($p< 0.05$ or 0.01) erythrocyte counts, hemoglobin levels, and hematocrit and increased MCV, MCH, abnormal erythrocyte forms, reticulocyte counts, and leukocyte counts (with no effect on differential counts) in mid- and/or high-dose males and females, and in low-dose females (#25% change for most parameters; 3-fold increase for reticulocytes). Hemolysis also led to increased (39-50%) plasma bilirubin in high-dose males and females. Consistent with erythrocyte damage, post-mortem gross examination showed a dose-related increase (18-220%) in spleen weight (absolute and relative to body) for all test groups at 12 and/or 24 months, and an increased incidence of spleen dark discoloration and/or swelling in mid and high-dose males and females after 12 and/or 24 months. Morphometric analysis of spleen sections to determine the percentage area of hemosiderin revealed an increase at $250 ppm in both sexes at 12 months and in all groups at 24 months ($p<0.05$ or 0.01), with the females being affected more severely. The chronic overburden of spleen function led to an increased incidence of spleen fibrosis in 2500 ppm males and females ($p<0.01$). Bone marrow activation occurred in both sexes at all test doses at 24 months ($p<0.05$ or 0.01 for all but low-dose females). This was evident morphometrically as an increase in hematopoietic (red) bone marrow for mid- and high-dose rats at 12 and/or 24 months (possibly in low-dose males at 12 months) with a concomitant decrease in fat marrow at 12 months (not evaluated at 24 months).

Gross pathology showed that the incidence of urinary bladder wall thickening was elevated at 24 months for low- and high-dose males and high-dose females ($p<0.05$ or 0.01). Microscopic evaluation showed that epithelial focal hyperplasia of the urinary tract and renal pelvis increased in severity in both sexes at 12 and/or 24 months, and increased in incidence ($p<0.01$) in high-dose males at 12 months and in mid and high-dose females at 12 and/or 24 months. Some gross and/or microscopic changes were also seen in the liver (increased weight, swelling, discoloration, vacuolar cell degeneration, round cell infiltration, hyperemia) although

these effects were not clearly primary effects of treatment.

Based on evidence of hemolytic anemia and compensatory hematopoiesis (decreased erythrocyte count, increased reticulocyte counts, increased spleen weight and bone marrow activation), the LOAEL is 25 ppm for both sexes of rats (1.0 and 1.7 mg/kg/day for males and females, respectively). A NOAEL was not established.

This chronic toxicity /carcinogenicity study in rats is classified as Acceptable/Guideline.

Dose and Endpoint for Establishing RfD: 1.0 mg/kg/day (LOAEL) based on evidence of hemolytic anemia and compensatory hematopoiesis (decreased erythrocyte count, increased reticulocyte counts, increased spleen weight and bone marrow activation). A NOAEL was not established.

Uncertainty Factor(s): 300

Comments about Study/Endpoint/Uncertainty Factor: An uncertainty factor (UF) of 100 is applied to account for both interspecies extrapolation and intra-species variability. An additional UF of 3 is applied for the use of a LOAEL.

Chronic RfD = $\frac{\text{1.0 (LOAEL) mg/kg/day}}{\text{300 (UF)}}$ = **0.003 mg/kg/day**

1.3 Occupational/Residential Exposure

1.3.1 Short-Term (1-7 days) Incidental Oral Exposure

Study Selected: Developmental toxicity study- rabbits § 870.3700

MRID No.: 40228802

Executive Summary: In a developmental toxicity study (MRID 40228802), 24-25 artificially inseminated New Zealand white rabbits per group were administered 0, 2, 10, or 50 mg/kg/day of Diuron (99% a.i.; Lot No. not given) by gavage on gestation days (GD) 7-19, inclusive. On GD 29, all surviving does were sacrificed and examined

grossly.

One control animal died on GD 0 due to an anaphylactic shock reaction during insemination and one high-dose doe aborted and was killed on GD 26. These deaths were considered unrelated to treatment. All remaining animals survived to scheduled termination. No treatment-related clinical signs of toxicity were observed in any animal. Maternal liver weights were comparable between the treated and control groups and gross necropsy was unremarkable.

Maternal body weights, body weight gains, and food consumption for the low- and mid-dose groups were similar to the control levels throughout the study. Absolute body weights of the high-dose does were significantly (p # 0.01) less than the controls on GD 20. Mean body weight gains by the high-dose group were significantly (p # 0.05 or 0.01) reduced as compared with the controls during the intervals of GD 10-13, 13-16, and 7-20 (weight loss). Weight gain by the high-dose group was significantly (p # 0.05 or 0.01) greater than the controls during the post-dosing interval. Food consumption by the high-dose group was significantly (p # 0.01) less than the controls during the GD 13-16, 16-20 and 7-20 intervals.

The maternal toxicity LOAEL is established at 50 mg/kg/day based on decreased body weights and food consumption during the dosing interval. The maternal toxicity NOAEL is established at 10 mg/kg/day.

At cesarean section, the pregnancy rates, numbers of corpora lutea, implantation sites, resorptions, and live fetuses, and fetal body weights were similar between the treated and control groups. No dose- or treatment-related external, visceral, or skeletal malformations/variations were observed in any fetus.

The developmental toxicity NOAEL is $50 mg/kg/day and the developmental toxicity LOAEL is not identified.

This study is classified as Acceptable and satisfy the guideline requirements for a developmental toxicity study [OPPTS 870.3700 (83-3b)] in rabbits.

Dose and Endpoint for Risk Assessment: 10 mg/kg/day (NOAEL) based on maternal toxicity (decreased body weights and food consumption during the dosing interval) at 50 mg/kg/day (LOAEL).

Comments about Study/Endpoint: This study was previously classified as

unacceptable/upgradable based on deficiencies in analytical data of sample analysis. However, the HIARC determined that this study is acceptable because the low nominal level of sample concentration was observed at the low dose only and the NOAEL was established at the mid-dose with the LOAEL at the high-dose. Therefore, the deficiencies in the analytical data did not affect the results of the study. The systemic toxicity (expressed as maternal toxicity) is relevant for the populations (infants and children) and duration (1-7 days) of concern.

1.3.2 Intermediate-Term (7 Days to Several Months) Incidental Oral Exposure

Study Selected: Chronic toxicity/carcinogenicity study- rats §

MRID No.: 40886501, 43871901, 43804501, 44302003

Executive Summary: See Chronic RfD.

Dose and Endpoint for Risk Assessment: A NOAEL of 1.0 mg/kg/day based on hematological effects observed at 10 mg/kg/day (LOAEL) at the 6th month observations.

Comments about Study/Endpoint: The HIARC established a NOAEL of 1.0 mg/kg/day for this time period based on hematological effects observed at 10 mg/kg/day at the 6th month observation. It is noted that this NOAEL/LOAEL is different from the 24th month observation where the NOAEL is not established (LOAEL=1.0 mg/kg/day). The endpoint observed at the 6th month observation period is appropriate for this exposure scenario and is relevant for the population of concern.

1.3.3 Dermal Absorption

No dermal absorption study is available.

Dermal Absorption Factor: An upper-bound estimation of dermal absorption factor of 4% is extrapolated using the maternal LOAEL of 50 mg/kg/day from the developmental study in the rabbit and the NOAEL of 1200 mg/kg/day (HDT) from the 21-day dermal toxicity study in the rabbit: the ratio is 50/1200 or 4%.

1.3.4 Short-Term Dermal (1-7 days) Exposure

Study Selected: None

MRID No.: N/A

Executive Summary: N/A

Dose and Endpoint for Risk Assessment: N/A

Comments about Study/Endpoint:. No systemic toxicity following repeated dermal dosing at 1200 mg/kg/day was seen in the rabbit dermal toxicity study. Also, there is no developmental concern. No hazard was identified and no quantitative assessment is required.

1.3.5 Intermediate-Term Dermal (7 Days to Several Months) Exposure

Study Selected: None

MRID No.: N/A

Executive Summary: N/A

Dose/Endpoint for Risk Assessment: N/A

Comments about Study/Endpoint: No systemic toxicity following repeated dermal dosing at 1200 mg/kg/day was seen in the rabbit dermal toxicity study. Also, there is no developmental concern. No hazard was identified and no quantitative assessment is required.

1.3.6 Long-Term Dermal (Several Months to Life-Time) Exposure

Study Selected: Chronic toxicity/carcinogenicity study- rats

MRID No.: 40886501, 43871901, 43804501, 44302003

Executive Summary: See chronic RfD.

Dose and Endpoint for Risk Assessment: 1.0 mg/kg/day (LOAEL) based on evidence of hemolytic anemia and compensatory hematopoiesis (decreased erythrocyte count,

increased reticulocyte counts, increased spleen weight and bone marrow activation). A NOAEL was not established.

Comments about Study/Endpoint: An additional UF of 3 is applied to account for the lack of a NOAEL in this study. A MOE of 300 is required for this risk assessment with a dermal absorption factor of 4%.

1.3.7 Inhalation Exposure

Except for an acute inhalation study, for which diuron was placed in Toxicity Category IV (LC_{50}>7.1 mg/L), no other studies are available via this route. Therefore, the HIARC selected the NOAELs from oral studies for risk assessment. Since the doses identified for inhalation risk assessment are from oral studies, route-to-route extrapolation should be as follows:

The inhalation exposure component (i.e., Fg a.i./day) using a 100% (default) absorption rate and application rate should be converted to an equivalent oral dose (mg/kg/day).

Then, the oral equivalent doses should be compared to the following NOAELs/LOAEL to calculate the MOEs.

Short-term	NOAEL= 10 mg/kg/day (developmental rabbit study)
Intermediated-term	NOAEL= 1.0 mg/kg/day (chronic rat study at 6 month)
Long-term	LOAEL= 1.0 mg/kg/day (chronic rat study)

1.3.8 Margins of Exposure for Occupational/Residential Risk Assessments

A MOE of 100 is adequate for short and intermediate-term occupational inhalation exposure. However, a MOE of 300 is required for long-term occupational dermal and inhalation exposure due to the use of LOAEL.
The acceptable MOEs for residential exposure will be determined by the FQPA SF committee.

1.4 Recommendation for Aggregate Exposure Risk Assessments

A toxicological endpoint was not identified for acute dietary risk assessment; therefore, the acute aggregate is not required.

A common toxicological endpoint (decreased body weight and food consumption) was

selected for assessment of short-term exposure by oral and inhalation routes. These routes can be aggregated for this scenario.

A common toxicological endpoint (altered hematological parameters) was selected for intermediated-term exposure by oral and inhalation routes. These routes can be aggregated for this scenario.

A common toxicological endpoint (evidence of hemolytic anemia and compensatory hematopoiesis) was selected for long-term exposure by oral, dermal, and inhalation routes. These routes can be aggregated for this scenario.

2 CLASSIFICATION OF CARCINOGENIC POTENTIAL

2.1 Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID No. 40886501, 43871901, 43804501, 44302003

Discussion of Tumor Data: **This study showed conclusive evidence for the carcinogenicity of diuron in male and female rats.** The incidence of urinary bladder carcinoma was increased at 2500 ppm in both sexes (males: 33/49 vs. 1/50 for controls; females: 11/50 vs. 0/48 for controls; $p<0.01$). The malignancies were usually characterized as transitional epithelial carcinomas. The slight increase (NS) in the incidence of urinary bladder papilloma and the 3 neoplasms in the renal pelvis in high-dose males (one papilloma and two carcinomas) were also considered treatment-related.

Adequacy of the Dose Levels Tested: Dosing was adequate based on numerous toxic effects (hematological, microscopic, etc.) observed in the animals at all tested doses.

2.2 Carcinogenicity Study in Mice

MRID No. : 42159501, 43349301

Discussion of Tumor Data: Treatment of up to 102 weeks with 2500 ppm diuron resulted in a significant increase in the incidences of mammary adenocarcinomas (control, 4%; 2500 ppm, 12%, p#0.05) and ovarian luteomas (control, 6%; 2500 ppm, 14%, p#0.01) in female NMRI (SPF HAN) mice under the conditions of this study. However, the incidence of mammary adenocarcinoma in high-dose females was at or near the high range of incidences seen in historic controls.

Adequacy of the Dose Levels Tested: Dosing was adequate based on observations at the highest dose tested including decreased body weight of both sexes, increased spleen and liver weights in males and increased incidence of urinary bladder edema and epithelial hyperplasia, thickened mucosa and enlarged uterine horn in females.

2.3 Classification of Carcinogenic Potential

The HED Carcinogenicity Peer Review Committee (CPRC) met on December 18, 1996 and classified diuron as a "known/likely" human carcinogen by all routes, based on urinary bladder carcinoma in both sexes of the Wistar rat, kidney carcinomas in the male rat (a rare tumor), and mammary gland carcinomas in the female NMRI mouse. The CPRC also recommended a low dose linear extrapolation model with Q_1^* $(mg/kg/day)^{-1}$ of $1.91x10^{-2}$ be applied to the animal data for the quantification of human risk, based on the urinary bladder carcinomas in the rat. The HIARC acknowledged that this classification may be re-evaluated by the CARC pending Registrant's submissions of mechanistic study for cancer.

3 MUTAGENICITY

Five acceptable genetic toxicology studies with Diuron have been submitted to the Agency. Findings from these studies indicated the following:

GENE MUTATIONS

1) *Salmonella typhimurium* reverse gene mutation assay (MRID No. 00146608/40228805): Independent trials were **negative** in *S. typhimurium* strains TA1535, TA97, TA98 and TA100 up to the highest does tested (10 µg/plate -S9; 250 µg/plate +S9); higher concentrations ($50 µg/plate -S9; 500 µg/plate +S9) were cytotoxic. The assay is **Acceptable** and satisfies the guideline requirement for gene mutation in microbial test systems.

2) Chinese Hamster Ovary (CHO)/HGPRT cell forward gene mutation assay (MRID No. 00146609): Independent tests were **negative** up to cytotoxic doses without S9 activation (1.250 mM, . 291 µg/mL) and with S9 activation (0.5 mM , . 117 µg/mL). The assay is **Acceptable** and satisfies the guideline requirement for gene mutation in cultured mammalian cells.

CHROMOSOME ABERRATIONS

3) *In vivo* bone marrow cytogenetic assay (MRID No. 00146611): The test was **weakly positive** in male Sprague Dawley rats administered 0, 50, 500 or 5000 mg/kg/day by single oral gavage. Signs of overt toxicity (mortality, body weight loss, ocular discharge, depression, labored respiration, diarrhea, and tremors) and cytotoxicity to the target organ (significantly decreased mitotic index) were seen at 5000 mg/kg in conjunction with a significant ($p<0.05$) increase in the percentage of abnormal cells when the data for both sexes were combined (0.11 versus 0.00 in controls). A significant positive linear trend ($p<0.01$) was also recorded for the percentage abnormal cells combined. A total of 4/10 animals in the high-dose group were affected: single chromatid breaks were seen in two males and one female and a chromatid fragment was seen in one male. This study is classified as **Acceptable** and satisfies the guideline requirement for *in vivo* cytogenetic mutagenicity data.

4) *In vivo* bone marrow cytogenetic assay (MRID No. 44350301): The test was **negative** in male Sprague Dawley rats administered 0, 50, 500 or 5000 mg/kg/day by single oral gavage. Signs of overt toxicity (mortality, body weight loss, ocular discharge, depression, labored respiration, diarrhea, and tremors) were noted at 5000 mg/kg. Cytotoxicity to the target organ as indicated by the significantly decreased (p#0.01) mitotic indices at 24 and 48 hours for high-dose males; data combined for both sexes were also significantly decreased at 24 hours. A significant ($p<0.05$) increase in the percentage of abnormal cells and the average number of aberrations per cell was seen but only when the data were combined for the high-and mid-dose males and females at the 48-hour sampling time. Values were 0.6 and 0.9 % (combined percentage abnormal cells) at 500 and 5000 mg/kg, respectively and 0.008 and 0.009 (combined number of aberrations/cell) at 500 and 5000 mg/kg, respectively. A significant positive linear trend was also recorded for the combined (by sex) aberrations per cell and percentage abnormal cells. Nevertheless, the values fell well within the range of historical control [percent abnormal cells/group: 0-2.6% (**%**) and 0-2.0% (**&**); average number of aberrations/cell: 0-0.023% (**%**) and 0-0.060 % (**&**)]. This study is classified as **Acceptable** and satisfies the guideline requirement for *in vivo* cytogenetic mutagenicity data.

OTHER MUTAGENIC MECHANISMS

4) Unscheduled DNA synthesis (UDS) in primary rat hepatocytes assay (MRID No. 00146610): The test was negative up to cytotoxic doses (**$**0.33 mM, equivalent to **.** 76 **F**g/mL). The assay is **Acceptable** and satisfies the guideline requirement for a UDS assay.

Conclusions: Diuron was not mutagenic in bacteria or in cultured mammalian cells and no indication of DNA damage in primary rat hepatocytes was observed. There was weak evidence of an *in vivo* clastogenic response in Sprague Dawley rats in one study and statistically significant increases in cells with structural aberrations in a second study conducted with the same rat strain. The data from the latter study, however, were shown to fall within the historical control range.

4 FQPA CONSIDERATIONS

4.1 Adequacy of the Data Base

The data base is adequate for FQPA assessment.

-- Acute delayed neurotoxicity study in hen: Not required.
-- Acute and subchronic neurotoxicity studies: Not available.
-- Developmental toxicity studies in Rats: Study was Unacceptable.
-- Developmental toxicity studies in Rabbits: Acceptable study available.
-- Two-Generation Reproduction Study in rats: Acceptable study available.
-- Developmental neurotoxicity study: Not available.

4.2 Neurotoxicity

No acute or subchronic neurotoxicity study is available. There are no neurotoxic signs in any of the subchronic or chronic studies. Literature search did not reveal studies relevant for assessing the potential neurotoxicity.

4.3 Developmental Toxicity

Developmental toxicity study in rabbits

See short-term incidental oral exposure.

Developmental toxicity study in rats

In a developmental toxicity study (MRID 40228801), 25 presumed pregnant Crl:COBS®CD®(SD)BR rats per group were administered H-16035 (99%; Lot No. not given) by gavage in 0.5% aqueous hydroxypropyl methylcellulose at doses of 0, 16, 80, or 400 mg/kg/day on gestation days (GD) 6-15, inclusive. On GD 20, dams were sacrificed, subjected to gross necropsy, and all fetuses were examined externally. Approximately one-half of all fetuses were examined viscerally by the Staples technique; these fetuses were decapitated, and the heads fixed in Bouin's solution for subsequent free-hand sectioning. The remaining one-half of the fetuses were eviscerated and all carcasses were processed for

skeletal examination.

All dams survived to terminal sacrifice. One high-dose animal appeared thin on GD 13-18 as a result of marked weight loss. No other treatment-related clinical signs of toxicity were observed in any group. Body weights, body weight gains, and food consumption by the low-dose group were similar to the controls throughout the study. No treatment-related lesions were observed in any dam at necropsy.

Absolute body weights of the mid- and high-dose groups were significantly (p # 0.01) less than the controls during the dosing interval and ranged from 92-94% and 84-88%, respectively, of the control levels. Body weight gains by the mid- and high-dose dams were significantly (p # 0.05 or 0.01) less than that of the controls during the dosing period with the exception of GD 12-16. The most pronounced effect on body weight gain occurred immediately after the initiation of dosing (GD 6-9) when the mid- and high-dose groups had a net weight loss compared to a gain by the controls. The high-dose group also had a weight loss for GD 9-12. Weight change during the entire dosing interval was 37% of the control level for the mid-dose group and a weight loss of 12.2 g by the high-dose group. Food consumption by the mid- and high-dose groups was significantly (73 and 47%, respectively, of controls; p # 0.01) less than the controls during the dosing interval. Weight gain and food consumption by the mid- and high-dose dams during the post-dosing period was significantly (p # 0.01) greater than the controls.

The maternal toxicity LOAEL is established at 80 mg/kg/day based on decreased body weights, body weight gains, and food consumption. The maternal toxicity NOAEL is 16 mg/kg/day.

No differences were observed between the treated and control groups for pregnancy rate, number of corpora lutea, number of implantation sites, number of fetuses/litter, or fetal sex ratios. No dead fetuses or late resorptions were observed. Two high-dose dams had total litter resorption and the number of early resorptions/dam in the high-dose group (3.2) was slightly greater than that of the controls (1.2). Mean fetal body weight in the high-dose group was significantly (p#0.01; 91% of controls) less than that of the controls.

In the 0, 16, 80, and 400 mg/kg/day groups, the total number of fetuses(litters) examined for external and skeletal malformations/variations was 288(22), 305(23), 297(22), and 279(20), respectively, and for visceral malformations/variations was 138(22), 149(23), 144(22), and 134(20), respectively. No treatment-related external or visceral malformations/variations were observed in any group.

Delayed ossification of the vertebrae and sternebrae was observed in fetuses of the high-dose group. In the 0, 16, 80, and 400 mg/kg/day groups the incidence rates for litters containing fetuses with bifid thoracic vertebral centra was 1/22, 1/23, 2/22, and 7/20 (p#0.05), respectively. Incomplete ossification of the sternebrae was observed in fetuses from 3/22, 3/23, 1/22, and 9/20 (p#0.05), litters respectively. Unossified thoracic vertebral centra was observed in fetuses from 3/20 (p # 0.05) high-dose litters but not in fetuses from the other treated or control groups.

The developmental toxicity LOAEL is established at 400 mg/kg/day based on whole litter resorption, reduced fetal body weights, and delayed ossification of the vertebrae and sternebrae. The developmental toxicity NOAEL is 80 mg/kg/day.

This study is classified as **Unacceptable** and **does not** satisfy the requirements for a developmental toxicity study [870.3700 (§83-3a)] in rats. Test article concentrations in the mid- and high-dose solutions were highly variable and well outside of acceptable ranges. Based upon available analytical data, it appears that target doses may not have been representative of the actual doses to the animals. In addition, the lot number and corresponding analyses were not provided. It is unlikely that this study may be upgraded.

However, the HIARC determined that this study is adequate for the assessment of susceptibility in rats. This decision was made based on the fact that maternal toxicity was seen at a lower dose (80 mg/kg/day) compared to developmental toxicity (400 mg/kg/day). At 400 mg/kg/say, developmental effects (increased incidence of early resorption and decreased fetal body weight) were seen in the presence of maternal toxicity (significantly decreased body weight gain and food consumption). The HIARC also determined that a repeat of this study is not required since the effects of the range-finding study showed maternal toxicity (decreased body weight gain and food consumption) at 100, 200, and 400 mg/kg/day and developmental toxicity (increased incidence of early resorption and decreased fetal body weight) at 400 mg/kg/day. Also, the rabbit was shown to be the more susceptible species for developmental toxicity study. A repeat rat study would not provide additional data for risk assessment/risk characterization.

4.4 Reproductive Toxicity

In a two-generation reproduction study Diuron (97.1% a.i., Lot No. 8805540) was administered to groups of 30 male and 30 female Crl:CD®BR rats in the diet at concentrations of 0, 10, 250, or 1750 ppm (MRID 41957301). One litter was produced by each generation. Test substance intake for the treated F_0 groups was 0.58, 14.8, and 101 mg/kg/day, respectively, for males and 0.71, 18.5, and 131 mg/kg/day, respectively, for females. Test substance intake for the treated F_1 groups was 0.77, 18.9, and 139 mg/kg/day, respectively,

for males and 0.8, 22.1, and 157 mg/kg/day, respectively, for females. F_0 and F_1 parental animals were administered test or control diet for 73 or 105 days, respectively, prior to mating and throughout mating, gestation, and lactation, and until necropsy.

Deaths or premature sacrifices of several F_0 and F_1 parental animals were considered incidental to treatment. No treatment-related clinical signs of toxicity were observed in the adult animals of either generation. Gross necropsy was unremarkable and testes weights were not affected by treatment.

For the low- and mid-dose groups of both generations, occasional significant differences from the control group for body weights, body weight gains, food consumption, and food efficiencies were considered incidental to treatment.

Body weights of the high-dose F_0 males and females were significantly (p # 0.05) decreased by an average of 7% beginning on day 7. Body weight gains by the high-dose F_0 males were significantly (p # 0.05) less than the control group on days 0-14, 21-28, 42-49, 77-84, and 91-98. Premating, post-mating, and overall (entire study) body weight gains by the F_0 males were significantly (p # 0.05) decreased by 16%, 28%, and 18%, respectively, compared with the controls. Body weight gains by the high-dose F_0 females were significantly (p # 0.05) less than the control group on days 0-14 and 21-28 with overall premating body weight gains significantly (p # 0.05) decreased by 28% compared with the controls. Significant (p # 0.05) reductions in food consumption were observed in the high-dose F_0 males and females on days 0-14, 21-28, 35-49 (females), 42-56 (males), and 0-70. Food efficiencies for the F_0 males and females were significantly (p # 0.05) reduced at similar intervals to food consumption with overall premating food efficiency reduced by 8.3% and 22.7%, respectively.

Body weights of the high-dose F_1 males and females were significantly (p # 0.05) decreased by an average of 16% beginning on day 0 of premating. Body weight gains by the high-dose F_1 males were significantly (p # 0.05) less than the control group on days 0-28, 42-49, 63-70, 91-98, and 147-154. Premating, post-mating, and overall (entire study) body weight gains by the F_1 males were significantly (p # 0.05) decreased by 15%, 41%, and 17%, respectively, compared with the controls. Body weight gains by the high-dose F_1 females were significantly (p#0.05) less than the control group on days 0-14 with overall premating body weight gains significantly (p # 0.05) decreased by 14% compared with the controls. Significant (p # 0.05) reductions in food consumption were observed in the high-dose F_0 males and females throughout premating with the exception of days 77-84 for males. Food efficiencies were significantly (p#0.05) reduced for the high-dose F_1 males on days 91-98 and for the high-dose F_1 females on days 0-7, 21-28, and 0-70.

The systemic toxicity LOAEL is 1750 ppm (approximately 132 mg/kg/day) based on reduced body weight, body weight gain, food consumption, and food efficiency during both generations. The systemic toxicity NOAEL is 250 ppm (approximately 18.6 mg/kg/day).

For the F_0 and F_1 females, reduced body weights and food consumption during gestation were considered a continuation of premating effects.

No treatment-related effects were noted in either generation on fertility indices, gestation length, pup survival, pup clinical observations, and pup anomalies. Pup body weights for sexes combined or separate were significantly (p#0.05) reduced in high-dose litters as compared with the controls throughout lactation for the F_1 pups and beginning on lactation day 7 for the F_2 pups.

The offspring toxicity LOAEL is 1750 ppm (approximately 132 mg/kg/day) based on decreased body weights of the F_1 and F_2 pups during lactation. The offspring toxicity NOAEL is 250 ppm (18.6 mg/kg/day).

The reproductive toxicity NOAEL is 1750 ppm (HDT).

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirements for a reproductive toxicity study [OPPTS 870.3800 (§83-4)] in rats.

4.5 Additional Information from Literature Sources

Literature searches have been conducted and no additional neurotoxicity, developmental or reproductive toxicity was found.

4.6 Determination of Susceptibility

Base on the developmental and reproductive toxicity studies, there was no evidence (qualitative or quantitative) for increased susceptibility following in utero and/or pre-/post-natal exposure.

4.7 Recommendation for a Developmental Neurotoxicity Study

There are no evidence that suggest requiring a developmental neurotoxicity study. The

developmental toxicity studies in rats and rabbits as well as the reproductive toxicity study in rats did not show any adverse effects below maternal or parental doses.

5 HAZARD CHARACTERIZATION

Diuron is a substituted urea herbicide for the control of a wide variety of annual and perennial broadleaved and grassy weeds on both crop and noncrop sites. The mechanism of action is the inhibition of photosynthesis. Diuron has a low acute toxicity (Tox. Cat. 3 or 4) by oral, dermal, or inhalation route exposure. Diuron is not an eye or skin irritant and not a skin sensitizer. A rat metabolism study indicated that diuron is rapidly absorbed and metabolized within 24 hours post-dose at low dose and within 48 hours post-dose at high dose. The urine is the major route of excretion in both sexes. A small amount of diuron is detected in the feces. The highest tissue residue levels were found in the liver and kidneys 4 days post ^{14}C-diuron dose. Metabolism of diuron involved N-oxidation, ring hydroxylation, demethylation, dechlorination, and conjugation to sulfate and glucuronic acid.

The primary diuron target organs are hematopoietic system and bladder (and renal pelvis). Erythrocyte damage resulted in hemolytic anemia and compensatory hematopoiesis, which are manifested as significantly decreased erythrocyte counts, hemoglobin levels, and hematocrit, and increased MCV, MCH, abnormal erythrocyte forms, reticulocyte counts, and leukocyte count. Consistent observations of erythocytic regeneration are seen in chronic toxicity studies in rats, mice and dogs. Gross pathology findings in chronic rat and mouse studies showed increased incidences of urinary bladder edema and wall thickening at high doses. Microscopic evaluation showed dose-related increases in the severity of epithelial focal hyperplasia of the urinary bladder and renal pelvis in both sexes.

Although the developmental toxicity studies in rats is classified unacceptable, the data base on diuron are adequate for pre- and post-natal toxicity evaluation and did not reveal developmental or reproductive toxicity. The NOAELs for maternal/parental toxicity were either less than or equal to the NOAELs for fetal or reproductive toxicity

The HED Carcinogenicity Peer Review Committee (CPRC) characterized diuron as a "known/likely" human carcinogen by all routes, based on urinary bladder carcinoma in both sexes of the Wistar rat, kidney carcinomas in the male rat (a rare tumor), and mammary gland carcinomas in the female NMRI mouse. The CPRC also recommended a low dose linear extrapolation model with Q_1^* $(mg/kg/day)^{-1}$ of $1.91x10^{-2}$ be applied to the animal data for the quantification of human risk, based on the urinary bladder carcinomas in the rat.

6 DATA GAPS

The HIARC determined that a 28 day inhalation study is required to address the concern for inhalation exposure potential based on the use pattern. The Registrant can follow the 90-day inhalation study protocol but cease exposure at 28 days. The HIARC also determined that a repeated chronic dog study is not required because a new study would not provide additional data since the observed effects are similar in the rat and the rat is the more sensitive species for this chemical.

7 ACUTE TOXICITY

Acute Toxicity of Diuron

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral	00146144	LD_{50} = 4721 mg/kg (M) >5000 mg/kg (F)	III
81-2	Acute Dermal	00146146	LD_{50} >2000 mg/kg	III
81-3	Acute Inhalation	40228803	LC_{50} >7.1 mg/L	IV
81-4	Primary Eye Irritation	00146147	At 48 hrs, all irritation had cleared.	III
81-5	Primary Skin Irritation	00146148	All irritation had cleared by 72 hrs.	IV
81-6	Dermal Sensitization	00146149	Nonsensitizer	N/A
81-8	Acute Neurotoxicity	N/A	Not available	N/A

8. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	There is no appropriate endpoint attributed to a single dose was identified. Therefore, an acute RfD was not established.		
Chronic Dietary	LOAEL = 1.0 UF = 300	Evidence of hemolytic anemia and compensatory hematopoiesis.	Chronic toxicity/carcinogenicity study in rats
		Chronic RfD = 0.003 mg/kg/day	
Cancer	Known/likely human carcinogen $Q_1^* = 1.91 \times 10^{-2}$	Urinary bladder carcinoma in both sexes of the Wistar rat, kidney carcinomas in the male rat (a rare tumor), and mammary gland carcinomas in the female NMRI mouse	Carcinogenicity study in rats and mice
Incidental Oral, short-Term	NOAEL= 10	Decreased body weight and food consumption	Developmental toxicity study in rabbits
Incidental Oral, Intermediate-Term	NOAEL = 1.0	Altered hematological parameters observed at 6 months.	Chronic toxicity/carcinogenicity study in rats
Dermal, Short-Intermediate-Term	No systemic toxicity following repeated dermal dosing at 1200 mg/kg/day was seen in the dermal toxicity study. Also, there is no developmental concern. No hazard was identified and no quantitative assessment is required.		
Dermal, Long-Term[a]	LOAEL = 1.0	Evidence of hemolytic anemia and compensatory hematopoiesis.	Chronic toxicity/carcinogenicity study in rats
Inhalation, Short-Term[b]	NOAEL = 10	Decreased body weight and food consumption	Developmental toxicity study in rabbits
Inhalation, Intermediate-Term[b]	NOAEL = 1.0	Altered hematological parameters observed at 6 months.	Chronic toxicity/carcinogenicity study in rats
Inhalation, Long-Term[b]	LOAEL = 1.0	Evidence of hemolytic anemia and compensatory hematopoiesis.	Chronic toxicity/carcinogenicity study in rats

a An oral endpoint was used for dermal exposure: dermal absorption factor of 4% of oral exposure shall be used.
b An oral endpoint was used for inhalation exposure: inhalation exposure assumed equivalent to oral exposure.